Applicants respectfully request that the claims be considered in view of the remarks contained herein.

I. AMENDMENT

Please make the following amendments:

In the Claims:

Please amend the claims, as follows:

47. (Thrice amended) A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) expressing a recombinant [providing an] opioid receptor polypeptide [wherein said opioid receptor polypeptide is] encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11 and selected from the group consisting of: (1) chimeric opioid receptors, (2) recombinant opioid receptor polypeptides[, wherein said opioid receptor polypeptides are] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:1 and (3) recombinant opioid receptor polypeptides[, wherein said opioid receptor polypeptides are] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

49. (Thrice amended) The process of claim 48, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the second extracellular loop of kappa [delta] opioid receptor.

50. (Thrice amended) A process of isolating a substance with an ability to act as a [specific] agonist of a kappa opioid receptor, said process comprising the steps of:

a) providing an opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11 and [wherein said opioid receptor polypeptide is] selected from the group consisting of: (1) chimeric opioid receptors, (2) recombinant opioid receptor polypeptides[, wherein said opioid receptor polypeptides are] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:1 and (3) recombinant opioid receptor polypeptides[, wherein said opioid receptor polypeptides are] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said opioid receptor polypeptide with a composition comprising said [candidate] substance;

c) detecting the ability of said [candidate] substance to [specifically] interact as an agonist with said opioid receptor polypeptide; and

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d) isolating said substance if the ability of said [candidate] substance to [specifically] interact with the opioid receptor polypeptide is detected.

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63. (Amended) The process of claim 59, wherein the opioid receptor polypeptide is [comprises] a chimeric opioid receptor polypeptide.

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66. (Amended) The process of claim 63, wherein the opioid receptor polypeptide comprises portions of both kappa and delta opioid receptors.

84. (Twice amended) A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

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a) expressing a recombinant [providing a] opioid receptor polypeptide [wherein said opioid receptor polypeptide is] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

85. (Amended) The process of claim 84, wherein said nucleic acid sequence [polynucleotide] comprises [a base sequence that is identical or complementary to a segment of] at least 40 contiguous bases of SEQ ID NO:1.

86. (Amended) The process of claim 84, wherein said nucleic acid sequence [polynucleotide] comprises [a base sequence that is identical or complementary to a segment of] at least 40 contiguous bases of SEQ ID NO:11.

87. (Amended) The process of claim 84, wherein said nucleic acid sequence [polynucleotide] comprises [a base sequence that is identical or complementary to a segment of] at least 55 contiguous bases of SEQ ID NO:1.

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88. (Amended) The process of claim 84, wherein said nucleic acid sequence [polynucleotide] comprises [a base sequence that is identical or complementary to a segment of] at least 55 contiguous bases of SEQ ID NO:11.

89. (Amended) The process of claim 84, wherein said nucleic acid sequence [polynucleotide] comprises [a base sequence that is identical or complementary to a segment of] at least 70 contiguous bases of SEQ ID NO:1.

90. (Amended) The process of claim 84, wherein said nucleic acid sequence [polynucleotide] comprises [a base sequence that is identical or complementary to a segment of] at least 70 contiguous bases of SEQ ID NO:11.

91. (Amended) A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) expressing a recombinant [providing an] opioid receptor polypeptide [wherein said opioid receptor polypeptide is] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:1;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

92. (Amended) The process of claim 91, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 40 contiguous bases of SEQ ID NO:1.

93. (Amended) The process of claim 92, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 50 contiguous bases of SEQ ID NO:1.

94. (Amended) The process of claim 93, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 75 contiguous bases of SEQ ID NO:1.

95. (Amended) The process of claim 94, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 100 contiguous bases of SEQ ID NO:1.

96. (Amended) The process of claim 95, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 680 contiguous bases of SEQ ID NO:1.

97. (Amended) A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) expressing a recombinant [providing an] opioid receptor polypeptide [wherein said opioid receptor polypeptide is] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

98. (Amended) The process of claim 97, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 40 contiguous bases of SEQ ID NO:11.

99. (Amended) The process of claim 98, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 50 contiguous bases of SEQ ID NO:11.

100. (Amended) The process of claim 99, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 75 contiguous bases of SEQ ID NO:11.

101. (Amended) The process of claim 100, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 100 contiguous bases of SEQ ID NO:11.

102. (Amended) The process of claim 101, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 680 contiguous bases of SEQ ID NO:11.

103. (Amended) A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

a) providing an opioid receptor polypeptide [wherein said opioid receptor polypeptide is] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:1;

b) contacting said opioid receptor polypeptide with a composition comprising said [candidate] substance;

c) detecting the ability of said [candidate] substance to [specifically] interact as an agonist with said opioid receptor polypeptide; and

d) isolating said substance if the ability of said [candidate] substance to [specifically] interact with the opioid receptor polypeptide is detected.

104. (Amended) The process of claim 103, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 40 contiguous bases of SEQ ID NO:1.

105. (Amended) The process of claim 104, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 50 contiguous bases of SEQ ID NO:1.

106. (Amended) The process of claim 105, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 75 contiguous bases of SEQ ID NO:1.

107. (Amended) The process of claim 106, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 100 contiguous bases of SEQ ID NO:1.

108. (Amended) The process of claim 107, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 680 contiguous bases of SEQ ID NO:1.

109. (Amended) A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

a) providing an opioid receptor polypeptide [wherein said opioid receptor polypeptide is] encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said opioid receptor polypeptide with a composition comprising said [candidate] substance;

c) detecting the ability of said [candidate] substance to [specifically] interact as an agonist with said opioid receptor polypeptide; and

d) isolating said substance if the ability of said [candidate] substance to [specifically] interact with the opioid receptor polypeptide is detected.

110. (Amended) The process of claim 109, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 40 contiguous bases of SEQ ID NO:11.

111. (Amended) The process of claim 110, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 50 contiguous bases of SEQ ID NO:11.

112. (Amended) The process of claim 111, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 75 contiguous bases of SEQ ID NO:11.

113. (Amended) The process of claim 112, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 100 contiguous bases of SEQ ID NO:11.

114. (Amended) The process of claim 113, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising [a base sequence that is identical or complementary to a segment of] at least 680 contiguous bases of SEQ ID NO:11.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

This application was filed May 31, 1995. The application is a divisional application of 08/292,694, filed August 19, 1994, which is currently pending. Claims 1-46 were cancelled and claims 47-80 were added by a Preliminary Amendment. In subsequent prosecution, claims 47-73 and 75-80 were elected following a Restriction Requirement dated October 29, 1996. In a Response to Official Action dated October 27, 1997, claims 53-58, 60-62, and 68-80 were withdrawn from consideration as non-elected species, and claims 81-90 were added. After all considered claims were rejected, Applicants amended some of the claims and added claims 91-114 in the Response to Official Action dated June 29, 1998. An Official Action dated August 13, 1999 (the "Action") rejected claims 47-49, 51, 59, 63-67, 81, and 83-114, and objected to claims 50, 52, and 82. Although claims 47-114 are pending, only claims 47-52, 59, 63-67, and 81-114 are the subject of this response.

Claims 47, 49, 59, 63, 66, 84-114 have been amended. Support for these amendments can be found at least at p.2, line 27; p. 9, lns. 33-35, p. 10, line 34; p. 12, line 30 to p. 13, line 15; and p. 14 lines 9-15. These amendments do not introduce material for which a new search by the Examiner is required.

B. Summary of the Invention

This invention involves Applicants' discovery of a process for screening for substances that interact with an opioid receptor. *See* Specification, p. 18, line 1 to p. 23, line 22 and p. 66 line 19-26, *inter alia*. This process can be accomplished by providing an opioid receptor polypeptide, contacting a candidate substance with the polypeptide, and detecting the ability of the substance to interact with the polypeptide. *See*, *inter alia*, Specification, p. 18, line 1 to p. 23, line 22 and p. 66, line 27 to p. 76, line 10. This invention has far-reaching implications for identification of substances such as agonists and antagonists of opioid receptors for use in diagnostic, drug design and therapeutic applications.

C. Substitute Declarations

Substitute Declarations were filed in application Serial Number 08/292,694, filed August 19, 1994, from which this present application is a divisional. Copies of this declaration are submitted herewith to correct the priority claim of this application. Foreign priority under 35 U.S.C. §119 (a-d) is **not** being claimed in this application. Application Serial Number 08/292,694 is a continuation of PCT/US94/05747 filed on May 20, 1994, which is a continuation-in-part of United States Patent Application Serial Number 08/147,592, filed November 5, 1993, which application is a continuation-in-part of United States Patent Application Serial Number 08/066,296, filed May 20, 1993. As can be discerned from the priority claim of the present application, priority is being claimed under 35 U.S.C. § **120** (since the application following the PCT was a continuation under 37 C.F.R. 1.53(b), not nationalization under 35 U.S.C. §371). Therefore, despite the Action's assertion to the contrary, *no foreign priority document needs to be submitted* in this case, as is indicated on Office Action Summaries dated October 27, 1997 and June 29, 1998.

D. Claims 47, 59, 63, 66, 84-91, 97, 103, and 109 Fulfill § 112, Second Paragraph

The Action rejects claims 47, 59, 63, 66, 84-91, 97, 103, and 109 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. The Action presents several arguments. Applicants respectfully traverse the rejection based on each of these arguments.

1. The Claimed Methods Are Useful

With respect to claims 47, 84, 91, and 97, the Action states it is not clear whether identifying test substances that interact with any opioid receptor would be useful. Applicants contend that usefulness is not a proper basis for asserting a rejection under section 112, second paragraph. Furthermore, as explained in more detail below, one of skill in the art would be able to distinguish what type of opioid receptor was binding to a candidate substance. Clearly, identifying a substance that interacted with a particular opioid receptor would be useful. Therefore, Applicants respectfully request that this rejection be withdrawn.

2. Claims 47 and 59 Are Definite

The Action further alleges claims 47 and 59 are vague and indefinite. Because step (a) recites providing "an opioid receptor polypeptide selected from the group consisting of," the Action contends that because groups of receptors were recited, it is unclear how many different receptors are provided for by this assay. It also alleges that the claims do not indicate whether the recombinant opioid receptor polypeptides are encoded by the same nucleic acid sequences. Applicants traverse this rejection.

Applicants point out that the phrase "a polypeptide...selected from the group consisting of: (1) chimeric opioid receptors...(2) recombinant opioid receptors..." is perfectly acceptable claim language even though the members are recited in the plural, as opposed to in their singular forms. One of skill in the art can understand the scope of the claim, which is sufficient to satisfy

the requirements of 35 U.S.C. § 112, second paragraph. Applicants request this rejection be withdrawn.

3. Claims 59, 103, and 109 Are Not Confusing

Claims 59, 103, and 109 are also said to be confusing because it is allegedly not clear whether the claimed invention is directed to a method of isolating an agonist of a kappa opioid receptor. The Action also questions whether step (b) requires a composition or a single substance because the step recites a composition but lists only one ingredient. These claims also use the term "specifically interact," which the Action contends is vague and indefinite since no definition is provided in the specification. Applicants respectfully traverse these grounds.

Step (b) in claims 59, 103, and 109 recites a "composition comprising said candidate substance," which particularly points out and distinctly claims the subject matter that the applicants regard as their invention. One skilled in the relevant art would clearly understand the phrase "composition comprising said candidate substance," even if only one ingredient is listed because the term "comprising" is used. Moreover, one skilled in the relevant art would understand the term "specifically interact" since it is a term of art that is used in the specification consistent with its well-known meaning, for example at page 11, lines 1-4. The specification also uses the word "selective" to be synonymous with "specific". *See e.g.,* Specification page 11, lines 1-8; page 27, lines 6-9. In the interests of furthering prosecution, however, Applicants have amended the claim to eliminate the word "specifically." Support for the meaning of the term "interact" can be found throughout the specification, for example, at page 10, lines 13-17; page 19, lines 1-5, as well as in the references cited by the Examiner, for example, in Frielle *et al.* at page 9498. Accordingly, Applicants respectfully request this rejection be withdrawn.

4. Claim 63, 66, and 85-90 Conform with Proper Patent Language

Furthermore, the Action contends that claim 63 is not clear as to whether the opioid receptor is the chimeric opioid receptor polypeptide of the recited alternative embodiment. Applicants have amended the claim to clarify its meaning.

Claim 66 is said to lack antecedent basis for "the polypeptide." Applicants believe there is antecedent basis for "the polypeptide," but the claim has been amended to further clarify that basis.

Claims 85-90 are alleged to lack antecedent basis for "said polynucleotide." These claims have been amended.

E. Claims 47-51, 59, 63, 66, 81, and 83-114 Are Enabled

Claims 47-51, 59, 63, 66, 81 and 83-114 are rejected under 35 U.SC. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention on several grounds. Applicants respectfully traverses each ground and addresses them individually below.

1. Plurality of Receptors Is Enabled

The Action alleges that claims 47 and 59 require exposing a test substance to a plurality of receptors because the claims do not limit the receptors to one having a specific amino acid sequence or encoded by a specific nucleotide sequence. Applicants traverse these grounds.

The test of enablement is whether the experimentation needed to practice the invention is undue. MPEP § 2164.01 (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). Applicants contend that the specification is enabled for the use of different opioid receptor polypeptides in the screening assays for the present invention. The disclosure teaches that all or portions of opioid receptors can be employed to screen and isolate substances that may be

interacting with a particular opioid receptor polypeptide. In doing so, the specification describes ligand binding assays in addition to studies that suggest that particular portions of the kappa and delta opioid receptors interact with ligands. Thus, the application discloses experiments and assays that allow one of skill in the art to screen for and isolate opioid receptor polypeptide ligands, as well as experiments that teach a skilled artisan how to identify portions of the opioid receptor that mediate the interaction. Applicants contend that the specification teaches how to use the claimed invention and that any experimentation required to practice the invention is routine because a significant amount of guidance and working examples is provided.

2. Opioid Receptor Polypeptides Are Enabled

The Action also alleged that the specification does not enable the claimed methods, which involve using a broad genus of opioid receptor polypeptides, particularly because the specification teaches that the second extracellular loop of the kappa opioid receptor is required for ligand binding. Applicants respectfully traverse.

Applicants contend that even though the specification may teach that the second extracellular loop of the kappa opioid receptor is involved in agonist binding, they cannot be required to limit their claims to preferred embodiments of their invention. Furthermore, fulfillment of the enablement requirement is simply that the "specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" MPEP 2164.08 (citing *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993)). Applicants disclose how to practice the claimed screening methods. Not only do they teach one of skill in the art about chimeric opioid receptors that include kappa opioid receptor sequences and human and mouse recombinant kappa opioid receptor

polypeptides but they also provide assays to determine whether an opioid receptor interacts with a ligand, both agonists and antagonists.

The Action also alleges that the claims are not enabled because the specification does not teach whether 10 amino acids of SEQ ID NO:2 or SEQ ID NO:12 are sufficient for ligand binding. Once again, Applicants emphasize that "[t]he test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." MPEP 2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976)). The specification discloses nucleic acid and polypeptide sequences for mouse and human kappa opioid receptors. It also discloses recombinant techniques for constructing and using chimeric kappa opioid receptors in binding assays. Applicants argue that one of skill in the art could subclone portions of the receptor based on the disclosure into chimeric molecules to test ligand binding. It would not require undue experimentation to determine whether a 10 amino acid segment would be sufficient. Based on this disclosure, one of skill in the art could practice the full scope of the invention without undue experimentation and consequently, Applicants respectfully request that this rejection be withdrawn.

3. Human Kappa Opioid Receptor of SEQ ID NO:11 Is Enabled

The Action contends that the claims recite the use of a polypeptide encoded by SEQ ID NO. 11, but it is not predictable that SEQ ID NO. 11 encodes either a functional receptor or the second extracellular loop of the human KAPPA opioid receptor, which is thought to be essential for ligand binding. Applicants respectfully traverse these grounds of the rejection.

The claims recite "opioid receptor polypeptides encoded for by a nucleic acid sequence comprising at least 30 contiguous bases" of SEQ ID NO:1 or SEQ ID NO:11. First, Applicants contend that one of skill in the art would appreciate that SEQ ID NO:11 encodes a functional

polypeptide by itself or could be used as a portion of a chimeric polypeptide. As shown in FIGS. 3, 4A and 4B, the human kappa opioid receptor polypeptide sequence disclosed in the specification has significant homology with the mouse amino acid sequence spanning from amino acid 87 to amino acid 380. Given that 292 residues of the human sequence are similar or identical to the corresponding mouse sequence, one of skill in the art would be able to practice the claimed invention based on the disclosure, which extensively discusses the mouse kappa opioid receptor polypeptide and chimeric molecules encoding portions of the mouse kappa opioid receptor.

Second, Applicants contend that there is evidence that the second extracellular loop is encoded by SEQ ID NO:11. The Specification at page 22, line 5, states that amino acids 167-228 correspond to the second extracellular loop. SEQ ID NO:11 encompasses this region, and thus, one of skill in the art would appreciate that SEQ ID NO:11 encodes the second extracellular loop. Nonetheless, as argued above, Applicants are not required to limit their claims to preferred embodiments because there is sufficient teaching in the application to allow one of skill in the art to practice the whole scope of the claimed invention, including the steps involving at least a portion of the human kappa opioid receptor.

Therefore, based on these arguments, Applicants respectfully request that the rejection based on these grounds be withdrawn.

4. Plurality of Receptors Is Enabled

Claims 47-52 and 81-102 are directed to a method of screening a substance for its ability to interact with an opioid receptor. The Action interprets these claims to be directed at identifying substances that interact with *any* opioid receptor, which might indicate a non-specific ligand. The Actions contends that without knowledge as to which opioid receptors with which

the ligand interacts, the substance determined by the claimed method would not be useful as a potential therapeutic agent or as a ligand in a binding assay. The Action also points to the preamble as not directed to determining whether a substance interacts with a specific opioid receptor. Applicants respectfully traverse.

Once again Applicants emphasize that the claims do not require a plurality of receptors, much less a plurality of varied receptors. The claims do not recite "any" opioid receptor. The claims instead recite an opioid receptor polypeptide "selected from the group consisting of (1) chimeric opioid receptor polypeptides, (2) recombinant opioid receptor polypeptides encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 and (3) recombinant opioid receptor polypeptides encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:11." First, one of skill in the art employing this assay may know the identity of the receptors used in it since that person specifically chose which receptors to use. The specification describes the use of more than one molecule of a particular opioid receptor polypeptide. For instance, in Examples 2 and 7, binding assays are performed in which clearly more than one polypeptide molecule is used. In Example 2, "cell membranes" that expressed a kappa opioid receptor polypeptide are used in the studies (emphasis added). One of skill in the art would appreciate not only that more than one cell membrane was used but also that more than one receptor may be on the cell membrane. Also, in Example 7, a skilled artisan would understand that the data presented in FIG. 10A and 10B represent binding results for numerous opioid receptor polypeptides, as opposed to a single opioid receptor polypeptide.

Second, even if the identity of a single type of receptor is not initially known or if a chimera is used, one of skill in the art would know how to identify which receptor polypeptide was interacting with the candidate substance. For example, various antibodies are described in

the specification as well as various assays utilizing them, which teaches one of skill in the art a way of identifying opioid receptor polypeptides. Thus, if a mixture of receptors were used in the claimed assay, one could determine which type of receptor may be binding a candidate ligand.

Finally, Applicants contend that even if a plurality of *different* opioid receptor polypeptides were employed in the methods of the claimed invention, one of skill in the art would already have in his possession the knowledge to distinguish these populations using, for example, protein detection assays involving antibodies. Alternatively, if a chimera were used, various controls could be implemented into the assay to determine which receptor polypeptide was actually interacting with a candidate ligand. Such controls can be derived the results of experiments described in the specification, for example, at page 151, where the ligand dynorphin inhibits activity of the chimera while naloxone does not. The skilled person could also implement the assays of the invention with a variegated population of receptor opioid polypeptides, do the binding assays, and then determine which polypeptides were mediating binding using these types of controls as well, for example, by using selective agonists or antagonists to distinguish between the polypeptides.

A skilled artisan would know how to practice the claimed invention without undue experimentation. Accordingly, Applicants respectfully request that this rejection be withdrawn.

5. Methods of Isolating a Kappa Opioid Receptor Agonist Are Enabled

Claims 59, 103, and 109 are alleged to be not enabled for isolating an agonist of a kappa opioid receptor because the claimed method step does not require providing a chimeric polypeptide that comprises the second extracellular loop of a kappa opioid receptor. Moreover, the Action contends that the method does not enable distinguishing between agonist and antagonist and as such, the claims are incomplete as method claims for determining that the

substance is agonist of a kappa opioid receptor. The claims have been amended to address some of these issues. Furthermore, one of skill in the art would know how to distinguish between an agonist and antagonist based on the teachings within the specification, for example, by the experiment demonstrated by FIG. 10, and by the references known to one of skill in the art at the time the application was filed. Applicants contend that determining whether a substance acted as an agonist or an antagonist would not require undue experimentation and thus the claim is adequately enabled by the specification. Accordingly, Applicants request that the rejection on this ground be withdrawn.

6. Claims Isolating a Kappa Opioid Receptor-Binding Compound Are Enabled

Claims 59, 103, and 109 require contacting the opioid receptor polypeptide with a composition comprising a substance. The Action alleges that if more than one compound present in the composition is capable of binding to the receptor, then the claims would not be enabled by the specification because they do not include a step for distinguishing the candidate compound from other compounds that might bind to a receptor. Applicants respectfully traverse this rejection.

The specification discloses various working examples of binding assays between an opioid receptor and an antagonist or agonist. For instance, in Example 2, binding studies are performed in which ligands are radiolabeled and their binding capacity to opioid receptors is assessed. Thus, a candidate compound may be labelled to allow for binding to be detected. One could also use the label to isolate it. Furthermore, specificity of binding is considered in the context of non-specific background. One of skill in the art would be able to isolate the compound based on its binding capabilities, for example, by using some type of binding affinity column and implementing the proper controls. There are many different types of assays that can

be employed to distinguish the compound that binds to the receptor from compounds that do not bind because the screening relies on a functional assay, which can be implemented throughout various steps of the claimed methods. Thus, one of skill in the art could practice the claimed invention without undue experimentation. Accordingly, Applicants respectfully request that this rejection be withdrawn.

F. Claims 47, 59, and 84-114 Are Not Anticipated by Ahmed *et al.*

The Action rejects claims 47, 59, and 84-114 under 35 U.S.C. § 102(b) as being anticipated by Ahmed *et al.* Even though the Action concedes that Ahmed does not teach the chimeric opioid receptor or a nucleic acid encoding the receptor, it still argues that Ahmed anticipates the claimed methods because the opioid receptor described in Ahmed is not functionally or structurally distinct from the claimed methods. Applicants respectfully traverse this rejection.

Claims 47, 84, 91, and 97 recite the step of "expressing a recombinant opioid receptor polypeptide" and claims 59 and 103 recite "isolating the substance." Ahmed *et al.* does not teach either of these steps. "Anticipation requires ***identity*** of the claimed process and a process of the prior art; the claimed process, ***including each step*** thereof, must have been described or embodied, either expressly or inherently, in a ***single reference***." *Glaverbal Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995) (emphasis added). Accordingly, because Ahmed *et al.* does not teach each element of the claimed invention, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

G. Claims 47 and 48 Are Nonobvious over Evans *et al.* in View of Frielle *et al.*

Evans *et al.* is said to disclose a method of screening for ligands that interact with the delta opioid receptor, while Frielle *et al.* is alleged to teach the use of chimeric β1/β2 adrenergic receptors in binding assays for determining the structure/function relationship of adrenergic

receptors. The Action contends it would have been obvious to modify the ligand binding assay of Evans by using the chimeric delta opioid receptor obtained by replacing a portion of the delta opioid receptor with that from the somatostatin receptor, as taught by Frielle, with the expectation of obtaining a chimeric opioid receptor that can be used in a ligand binding assay. Applicants respectfully traverse this rejection.

The rejected claims are directed to a method that employs an "opioid receptor polypeptide [that] comprises a base sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11." Applicants contend that a proper *prima facie* obviousness rejection cannot be made against the claims because "the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2142. Neither Frielle *et al.* nor Evans *et al.* teaches such an opioid receptor polypeptide. Accordingly, the combination of these references does not establish that the claimed invention is obvious.

Applicants also maintain that there is simply no motivation to combine Frielle *et al.* and Evans *et al.* The Action concedes that Evans *et al.* does not disclose a method of screening using a chimeric delta opioid receptor, but contends that there is a motivation to use chimeric delta opioid receptors in the assay because one of skill in the art would appreciate that using different receptors in the assay would provide a larger number of ligands. Applicants challenge the Examiner's reliance on this reason as providing the adequate motivation required to establish a *prima facie* obviousness rejection. None of the cited references motivates or suggests their combination as is required. MPEP 2142. Thus, the Action implies that it is within the capacity of one of skill in the art to provide his own motivation to combine these two references.

"The prior art must provide a motivation or reason for the worker in the art, without the applicant's specification, to make the necessary changes in the reference device." *Ex Parte*

Chicago Rawhide Mfg. Co., 226 U.S.P.Q. 438 (PTO Bd. App. 1984). Applicants contend that the Action improperly relies on the specification as a blueprint to solve the problem and requests that the Examiner provide a document to bolster her contention that one of skill in the art would appreciate the combination of Evans *et al.* and Frielle *et al.* without a suggestion or motivation within the documents.

In fact, it appears the rejection is rooted in impermissible hindsight. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, where no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983). The Action asserts that one of skill in the art would combine the references because that person would want to identify more ligands. Of course, the specification teaches not only the idea that the compositions of the invention can be used, but also how additional ligands can be identified. Without this disclosure, one of skill in the art would not have the tools or the know how to make and use the claimed invention.

Based on the these arguments, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

H. Claims 50, 52, and 82 Are Not Objectionable

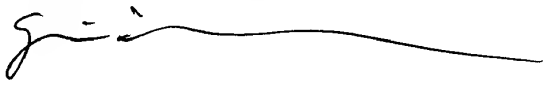
Claims 50, 52, and 82 were objected to as depending from a rejected base claim. Applicants believe the claims upon which they depend have been placed in condition for allowance and respectfully request that this objection be withdrawn.

I. Conclusion

Applicant has submitted remarks that are believed to place the present claims in condition for allowance. In view of this, Applicant respectfully requests that the present claims be passed for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicant's representative listed below at (512) 418-3081.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,



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47. A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) expressing a recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11 and selected from the group consisting of: (1) chimeric opioid receptors, (2) recombinant opioid receptor polypeptides encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 and (3) recombinant opioid receptor polypeptides encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

48. The process according to claim 47, wherein said opioid receptor polypeptide is a chimeric opioid receptor polypeptide.

49. The process of claim 48, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the second extracellular loop of kappa opioid receptor.

50. The process of claim 48, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of kappa opioid receptor.

51. The process of claim 48, wherein the chimeric opioid receptor polypeptide comprises polypeptide portions of both kappa and delta opioid receptors.

52. The process according to claim 48, wherein said chimeric opioid receptor polypeptide is designated as $\kappa_{1\text{-}78}/\delta_{70\text{-}372}$ or $\delta_{1\text{-}69}/\kappa_{79\text{-}380}$.

53-58. [Withdrawn as to non-elected invention]

59. A process of isolating a substance with an ability to act as a agonist of a kappa opioid receptor, said process comprising the steps of:

a) providing an opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11 and selected from the group consisting of: (1) chimeric opioid receptors, (2) recombinant opioid receptor polypeptides encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 and (3) recombinant opioid receptor polypeptides encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said opioid receptor polypeptide with a composition comprising said substance;

c) detecting the ability of said substance to interact as an agonist with said opioid receptor polypeptide; and

d) isolating said substance if the ability of said substance to interact with the opioid receptor polypeptide is detected.

60-62. [Withdrawn as to non-elected invention]

63. The process of claim 59, wherein the opioid receptor polypeptide is a chimeric opioid receptor polypeptide.

64. The process of claim 63, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the second extracellular loop of kappa opioid receptor.

65. The process of claim 63, wherein one polypeptide of the chimeric opioid receptor polypeptide comprises the third extracellular loop of delta opioid receptor.

66. The process of claim 63, wherein the opioid receptor polypeptide comprises portions of both kappa and delta opioid receptors.

67. The process of claim 63, wherein said chimeric polypeptide is designated as $\kappa_{1-78}/\delta_{70-372}$ or $\delta_{1-69}/\kappa_{79-380}$.

68-80. [Withdrawn as to non-elected invention]

81. The process according to claim 47, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide having the sequence of SEQ ID NO:2 or SEQ ID NO:12.

82. The process of claim 81, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide encoded for by the polynucleotide of SEQ ID NO: 1.

83. The process of claim 81, wherein said opioid receptor polypeptide is a kappa opioid receptor polypeptide encoded for by the polynucleotide of SEQ ID NO: 11.

84. A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) expressing a recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1 or SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

85. The process of claim 84, wherein said nucleic acid sequence comprises at least 40 contiguous bases of SEQ ID NO:1.

86. The process of claim 84, wherein said nucleic acid sequence comprises at least 40 contiguous bases of SEQ ID NO:11.

87. The process of claim 84, wherein said nucleic acid sequence comprises at least 55 contiguous bases of SEQ ID NO:1.

88. The process of claim 84, wherein said nucleic acid sequence comprises at least 55 contiguous bases of SEQ ID NO:11.

89. The process of claim 84, wherein said nucleic acid sequence comprises at least 70 contiguous bases of SEQ ID NO:1.

90. The process of claim 84, wherein said nucleic acid sequence comprises at least 70 contiguous bases of SEQ ID NO:11.

91. A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) expressing a recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

92. The process of claim 91, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 40 contiguous bases of SEQ ID NO:1.

93. The process of claim 92, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 50 contiguous bases of SEQ ID NO:1.

94. The process of claim 93, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 75 contiguous bases of SEQ ID NO:1.

95. The process of claim 94, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 100 contiguous bases of SEQ ID NO:1.

96. The process of claim 95, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 680 contiguous bases of SEQ ID NO:1.

97. A process of screening a substance for its ability to interact with an opioid receptor, said process comprising the steps of:

a) expressing a recombinant opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said substance with the opioid receptor polypeptide; and

c) detecting the ability of said substance to interact with said opioid receptor polypeptide.

98. The process of claim 97, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 40 contiguous bases of SEQ ID NO:11.

99. The process of claim 98, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 50 contiguous bases of SEQ ID NO:11.

100. The process of claim 99, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 75 contiguous bases of SEQ ID NO:11.

101. The process of claim 100, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 100 contiguous bases of SEQ ID NO:11.

102. The process of claim 101, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 680 contiguous bases of SEQ ID NO:11.

103. A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

a) providing an opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:1;

b) contacting said opioid receptor polypeptide with a composition comprising said substance;

c) detecting the ability of said substance to interact as an agonist with said opioid receptor; and

d) isolating said substance if the ability of said substance to specifically interact with the opioid receptor is detected.

104. The process of claim 103, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 40 contiguous bases of SEQ ID NO:1.

105. The process of claim 104, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 50 contiguous bases of SEQ ID NO:1.

106. The process of claim 105, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 75 contiguous bases of SEQ ID NO:1.

107. The process of claim 106, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 100 contiguous bases of SEQ ID NO:1.

108. The process of claim 107, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 680 contiguous bases of SEQ ID NO:1.

109. A process of isolating a substance with an ability to act as a specific agonist of a kappa opioid receptor, said process comprising the steps of:

a) providing an opioid receptor polypeptide encoded for by a nucleic acid sequence comprising at least 30 contiguous bases of SEQ ID NO:11;

b) contacting said opioid receptor polypeptide with a composition comprising said substance;

c) detecting the ability of said substance to interact as an agonist with said opioid receptor polypeptide; and

d) isolating said substance if the ability of said substance to interact with the opioid receptor polypeptide is detected.

110. The process of claim 109, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 40 contiguous bases of SEQ ID NO:11.

111. The process of claim 110, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 50 contiguous bases of SEQ ID NO:11.

112. The process of claim 111, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 75 contiguous bases of SEQ ID NO:11.

113. The process of claim 112, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 100 contiguous bases of SEQ ID NO:11.

114. The process of claim 113, wherein said opioid receptor polypeptide is encoded for by a nucleic acid sequence comprising at least 680 contiguous bases of SEQ ID NO:11.